Pediatric Nutrition
CONTINUING EDUCATION FOR CLINICIANS

COURSE TRANSCRIPT

Neonatal Resuscitation: Scientific Basis

Miami Neonatology 2019—43rd Annual International Conference

Overview

Extremely preterm infants are unique among neonates. **Satyan Lakshminrusimha, MD,** discusses asphyxia and resuscitation, while reviewing the clinical and translational science and current guidelines in the care of these preterm infants. **Dr. Lakshminrusimha** elaborates on the vital elements of effective neonatal resuscitation, cord clamping and milking, decreasing the risk of IVH, and the optimum oxygen levels for initial resuscitation of extremely preterm infants. Recommended umbilical vein epinephrine dosing is reviewed for more effective in resuscitation.

Target Audience

This activity was developed for neonatologists, pediatric physicians, nurses, nurse practitioners, dietitians, and other health care providers who have an interest in newborns, infants and toddlers.

Learning Objectives

At the conclusion of this activity, participants should be better able to:

- Understand the pathophysiology of asphyxia and the response for effective resuscitation
- Review the clinical and translational science supporting or refuting current guidelines.

Faculty

Satyan Lakshminrusimha, MD
Professor and Chair of Pediatrics
Pediatrician-in-Chief
UC Davis Children's Hospital
Sacramento, California

Accreditation and Certification

The Annenberg Center for Health Sciences at Eisenhower is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

The Annenberg Center for Health Sciences at Eisenhower designates this enduring material for a maximum of 1.0 *AMA PRA Category 1 Credit*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

AANP PROVIDER | American Association of NURSE PRACTITIONERS

Annenberg Center for Health Sciences at Eisenhower is accredited by the American Association of Nurse Practitioners as an approved provider of nurse practitioner continuing education. Provider number: 040207.

This program is accredited for 1.0 contact hour.
Program ID #5709-1EM

Annenberg Center for Health Sciences is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

A maximum of 1.0 contact hour may be earned for successful completion of this activity.

Provider is approved by the California Board of Registered Nursing, Provider #13664, for 1.0 contact hour. To receive credit for education contact hours outside of the state of California, please check with your state board of registered nursing for reciprocity.

Annenberg Center for Health Sciences at Eisenhower is a Continuing Professional Education (CPE) Accredited Provider with the Commission on Dietetic Registration (CDR). Registered dietitians (RDs) and dietetic technicians, registered (DTRs) will receive 1.0 continuing professional education unit (CPEU) for completion of this program/material.
Provider number: AC857
Activity number: 153641

Learners may submit additional evaluations of the quality of this program/material at cdr@eatright.org.

Neonatal Resuscitation: Scientific Basis

Disclosure Statement

It is the policy of the Annenberg Center for Health Sciences to ensure fair balance, independence, objectivity, and scientific rigor in all programming. All faculty and planners participating in sponsored programs are expected to identify and reference off-label product use and disclose any relationship with those supporting the activity or any others with products or services available within the scope of the topic being discussed in the educational presentation.

The Annenberg Center for Health Sciences assesses conflict of interest with its instructors, planners, managers, and other individuals who are in a position to control the content of CE/CME activities. All relevant conflicts of interest that are identified are thoroughly vetted by the Annenberg Center for fair balance, scientific objectivity of studies utilized in this activity, and patient care recommendations. The Annenberg Center is committed to providing its learners with high-quality CE/CME activities and related materials that promote improvements or quality in health care and not a specific proprietary business interest of a commercial interest.

In accordance with the Accreditation Council for Continuing Medical Education Standards, parallel documents from other accrediting bodies, and Annenberg Center for Health Sciences policy, the following disclosures have been made:

Satyan Lakshminrusimha, MD, has no relevant financial relationships to disclose.

The faculty for this activity has disclosed that there will be no discussion about the use of products for non-FDA approved indications.

Additional content planners

The following have no significant relationships to disclose:

Erin Allen, MS, RD, LDN (RD reviewer)
Victoria Anderson (medial writer)
Heather M. Jimenez, FNP (nurse reviewer)

Annenberg Center for Health Sciences

Charles Willis, Director of Continuing Education, consults for Pfizer, Inc., all other staff at the Annenberg Center for Health Sciences at Eisenhower have no relevant commercial relationships to disclose.

The ideas and opinions presented in this educational activity are those of the faculty and do not necessarily reflect the views of the Annenberg Center and/or its agents. As in all educational activities, we encourage practitioners to use their own judgment in treating and addressing the needs of each individual patient, taking into account that patient's unique clinical situation. The Annenberg Center disclaims all liability and cannot be held responsible for any problems that may arise from participating in this activity or following treatment recommendations presented.

This activity is supported by an independent educational grant from **Mead Johnson Nutrition**.

This activity is an online enduring material. Successful completion is achieved by reading and/or viewing the materials, reflecting on its implications in your practice, and completing the assessment component.

The estimated time to complete the activity is 1.0 hour.

This activity was released on February 7, 2020 and is eligible for credit through February 7, 2022.

Contact Information

For help or questions about this activity please contact Continuing Education:
ce@annenberg.net

Neonatal Resuscitation: Scientific Basis

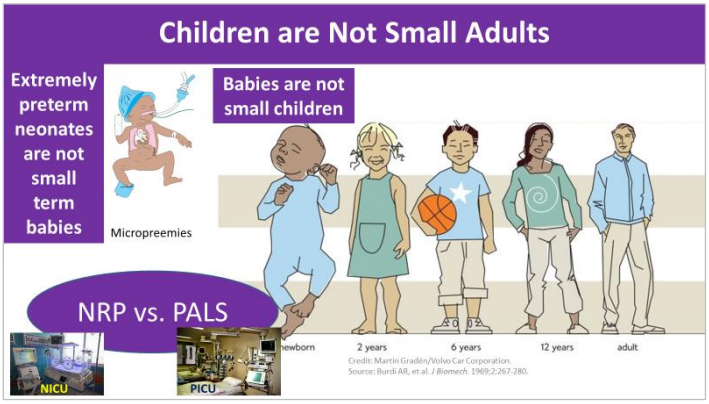
Editor's Note: This is a transcript of a live presentation on November 11, 2019, at the Miami Neonatology International Conference. It has been edited and condensed for clarity.

Satyan Lakshminrusimha, MD: I'll be talking to you about neonatal resuscitation. We'll talk both about term infants and preterm infants. I'm a member of the NRP [Neonatal Resuscitation Program] Steering Committee, but many of the thoughts I express are my own and do not reflect the position of either AAP [American Academy of Pediatrics] or the NRP.

I'll briefly talk about asphyxia and resuscitation and review clinical and translational science supporting or refuting the current guidelines.

Extremely Preterm Infants Are Unique

The day I joined my residency in pediatrics in Brooklyn, my chair told us that children are not small adults. Then when I joined [my] neonatal fellowship, I was told that babies are not small children. By the time I finished my neonatal fellowship, I realized that micro-preemies are not small term babies. In fact, I believe micro-preemies are aliens who do not follow any physiologic principles whatsoever known to neonatology.



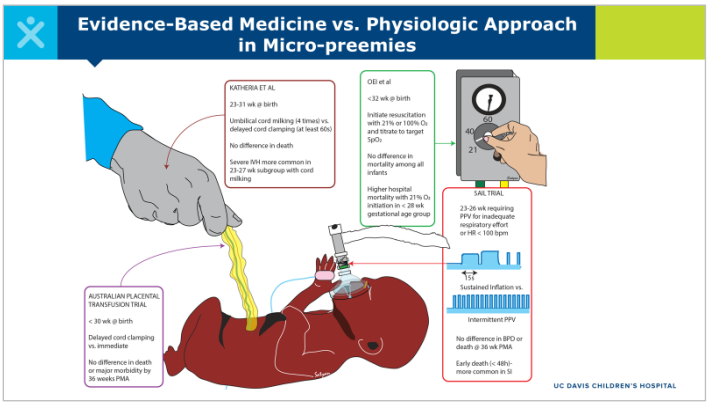
Slide 1

This is clearly reflected in how we deal with what resuscitation program we use while taking care of babies, whether it should be to use NRP or PALS [Pediatric Advanced Life Support], and this is a question that comes up very often. For example, if you see a 6-month-old baby with BPD [bronchopulmonary dysplasia] in the NICU, this baby receives resuscitation using NRP guidelines. On the other hand, if you see [a baby] at 3-days old in the PICU, post cardiac surgery or in preparation for cardiac surgery, this baby will receive resuscitation using PALS guidelines. This has been a huge controversy as to what we should use and what is more appropriate. There is, in fact, a task force from the AAP/NRP committee trying to address this question, and hopefully we'll have some answers soon.

I will illustrate the example as to why preemies don't follow any of the rules, using some of the recent evidence-based medicine studies.

Based on physiology, we assume a few things, and unfortunately these don't stand out when you do proper randomized clinical trials. Say, for example, if you take the TORPEDO trial,[1] we knew full well from term infants that 21% oxygen is great for term babies, but preterm babies, no, it did not work. In fact, there was **higher mortality in babies less than 28-weeks' gestation when they use 21% O_2**. Similarly, if you look at the SI [sustained inflation], the SAIL [Sustained Aeration Inflation for Infant Lungs] study,[2] contrary to all physiologic data based in animal studies, it turned out that using sustained inflation in preterm babies, especially extremely preterm babies, caused increased mortality in the first 48 hours.

Neonatal Resuscitation: Scientific Basis

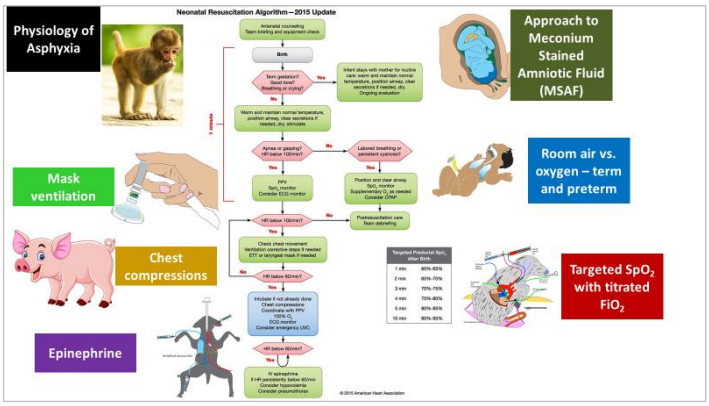


Slide 2

Cord Clamping and Milking

If we move on to the Australian Placental Transfusion Trial,[3] here delayed cord clamping was associated with some benefit, but when you adjusted for all the factors, and corrected for statistical variations, there was no difference in primary outcome between delayed cord clamping and immediate cord clamping in premature infants. And finally, a new criteria presented data at the 2019 PAS meeting showing that in babies—extremely preterm infants— umbilical cord milking was associated with increased risk of interventricular hemorrhage.[4] These trials clearly show that whatever you learn from animal-based studies, using physiology may or may not apply when we do evidence-based trials and randomized clinical trials. This is especially true with micro-preemies.

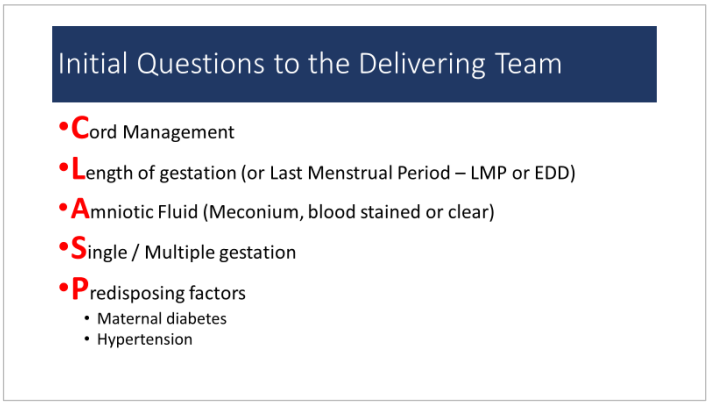
Here is the NRP algorithm, and for many years we have learned many aspects of this algorithm, and many of them are based on animal trials. For example, the primary apnea and secondary apnea that we read so much about is all from rhesus monkeys. Thankfully meconium-stained amniotic fluid data is mostly from human infants. We have data on room air vs oxygen, both in term and preterm infants, also from human infants. Data on targeted FiO_2 is mostly done in lambs. Data on mass ventilation and some chest compression ventilation is just compressions done mostly in piglets. Finally, most of the information that we have about epinephrine comes from lambs, as well. This NRP guideline is based loosely on data from adults, data from animals, and some randomized trials in humans.



Slide 3

Placental Transfusion

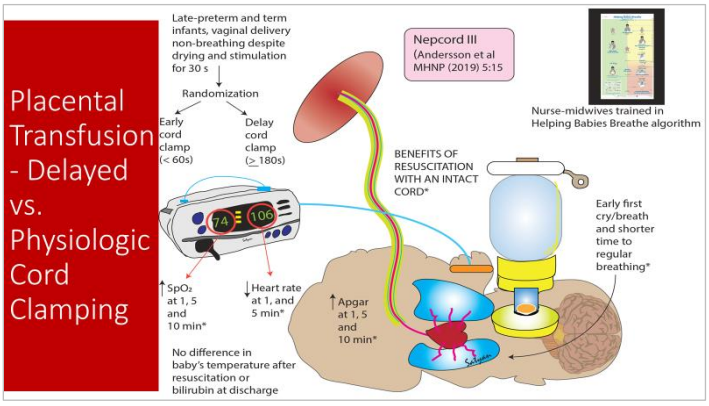
When you go to the delivery room, we typically ask 3 questions, but now it's really, really important to ask the first question with the obstetrician: **How do we plan on managing the cord?** Or what is the plan for cord management? Are we planning on doing delayed cord clamping? Immediate cord clamping? Or, are we planning on milking the cord? This needs to be clarified before you start the delivery, and this is a very important aspect.



Slide 4

Neonatal Resuscitation: Scientific Basis

Placental transfusion is really important, and there is quite a bit of controversy about the right term—physiological cord clamping vs placental transfusion vs delayed cord clamping. But the basic premise is that **almost a third of fetal blood is still in the placenta at the time of birth**, and that rightfully belongs to the fetus **and should come over to the fetus.** This can happen if you delay the cord clamping long enough for pulmonary circulation to be established.



Slide 5

The other important thing to remember is that uterine contractions in a spontaneous vaginal delivery generate almost [one] hundred mm of mercury pressure that squeezes the placenta and pushes the blood into the fetus. As Dr. Van Kaam was mentioning earlier, the height or the role of gravity in a spontaneous vaginal delivery with good nutrient contractions is immaterial. The baby might be on the maternal abdomen, or just below the introitus, and [that] doesn't make a difference because the uterus is contracting with such great force, it would propel blood from the placenta into the baby. On the other hand, if the uterus is atonic, and it's an elective C-section, then we are not really sure how this works. Gravity might play a role in those associations, and that's not really well studied, yet.

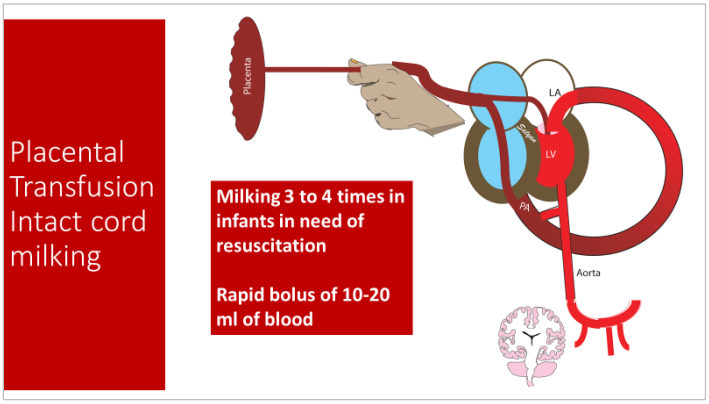
The second thing to remember is that if you use delayed cord clamping, the umbilical vein drains more blood into the baby. That usually enters the pulmonary circulation because the pulmonary circulation is starting to dilate with spontaneous breathing by the baby. By the same token, the umbilical artery is still open, so the afterload is not very high on the left ventricle. That helps the left ventricle function better in these situations, and that can accommodate and provide plenty of blood supply with increased oxygen level to the baby's brain. However, delayed cord clamping typically is defined in various ways in different studies. In general, delaying for more than 30 seconds is considered to be delayed in some studies—often it's 60 seconds—but as Dr. Van Kaam showed us earlier, it may need to be as long as 5 minutes in some patients. Each baby is very different.

If a baby requires aggressive resuscitation, how do we practice delayed cord clamping? There are several studies looking at this, but one recent [study] that came out is the Nepcord III trial that was conducted in Katmandu in Nepal by Ola Andersson and his colleagues.[5] They showed that if you delayed early cord clamping vs delayed cord clamping, and used helping-babies-breathe-resuscitation module, and resuscitate these babies with room air using a self-inflated bag, that resulted in better SpO_2 at 1, 5, and 10 minutes, which was the primary outcome in these babies. So, resuscitating babies with an intact cord is feasible, and it works fairly well with delayed cord clamping or physiological cord clamping.

Cord Milking

What about cord milking? There are 2 types of cord milking. One is intact cord milking, where the placenta...umbilical cord is still attached to the placenta, and then you milk, and then blood comes over and enters the baby. There are some advantages in that this is rapid. It doesn't take as long as delayed cord clamping, but as was mentioned earlier, each of these milking episodes can result in a rapid bolus of 10 mL–20 mL of blood

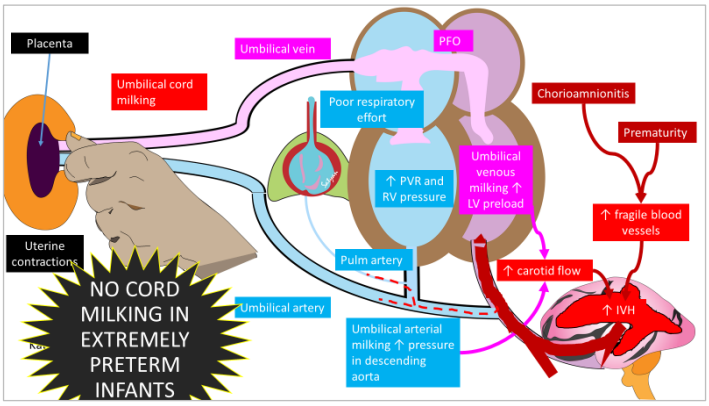
into the baby, and that might be too much in some circumstances.



Slide 6

If it's a term baby who is breathing spontaneously... these babies have an open pulmonary circulation, and when the pulmonary circulation is open, these babies can accommodate this increased blood much more effectively than when the baby is not spontaneously breathing. This is clearly shown in Anup Katheria's trial, which I will definitely talk to you about,[4] where the incidence of IVH was significantly higher in preterm babies who underwent cord milking. So, why does this happen?

Here is the placenta being squeezed by the uterus [Slide 7], and here are uterine contractions. If you milk the umbilical cord in this situation, you are not only milking the umbilical vein that pushes blood into the baby, you're also milking the umbilical artery, and each of those has different consequences.



Slide 7

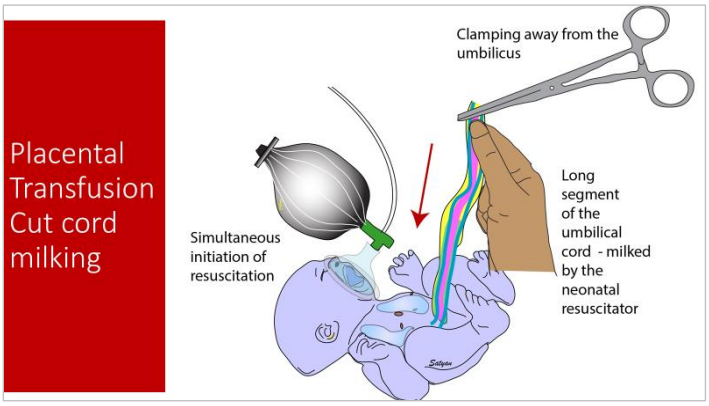
Decreasing Risk of IVH

If you milk the umbilical vein, what happens is more blood enters the left ventricle, increasing the preload. You need to remember that in babies who are not spontaneously breathing, or do not have good respiratory effort, the pulmonary vascular resistance remains high, and so the right ventricular pressure remains high. This increased blood, coming back from the umbilical vein, promptly crosses the ovale foramen and fills up the left ventricle, contributing to left ventricular preload, which is good. By the same token, since you're milking the umbilical artery, the pressure in the umbilical in the descending aorta is high because this is blocking and increasing the afterload on the left ventricle. In addition, many of these babies who developed IVH [intraventricular hemorrhage] in Katheria's trial also had chorioamnionitis and were extremely preterm.[4] Both these conditions contribute to increased fragility of the cerebral vessels, especially the germinal matrix.

In this situation, where you have high pulmonary vascular resistance, high afterload in the descending aorta because of umbilical arterial milking, if you increase carotid blood flow, this blood cannot enter the descending aorta and cannot cross the ductus arteriosus to the pulmonary artery, and most of it perfuses the brain. This increased fluctuation in blood pressure of the

cerebral circulation can give rise to intracerebral hemorrhage in these babies. We suspect that this is one of the causes for increasing interventricular hemorrhage. The classic triad here is actually in prematurity, presence of maternal chorioamnionitis, and poor spontaneous respiratory effort from the preterm infant. At this time, **until we have more studies, it's recommended that we do not pursue cord milking in extremely preterm infants** because of the increased risk of intraventricular hemorrhage in this particular study.[4]

The second method of cord milking is cut-cord milking, where you cut the umbilical cord 20, 30 cm away from the baby, and then you milk it on the radiant warmer. This is something practiced a lot in Japan, and there are some studies to show that it's quite effective, as well.[6]

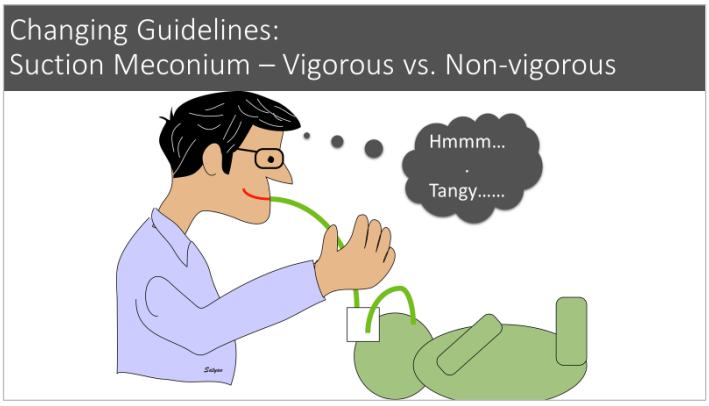


Slide 8

Meconium-Stained Amniotic Fluid

Let's move along to probably the most controversial area, meconium-stained amniotic fluid. Every time I give a talk on neonatal resuscitation, many in the audience are very upset about the new guidelines for meconium, and that continues to be a hot button issue to this day.

How many of you here have used the DeLee suction apparatus to suck meconium? Let me see a show of hands. Oh, very few. I'm disappointed. For those of you who haven't had the pleasure of tasting meconium, it tastes a little tangy. It almost tastes like guacamole with a pinch of salt, and a bit of lime in it. It's worth tasting... once. When I trained in India, as well as here, we had all these rules for managing mothers with meconium-stained amniotic fluid.

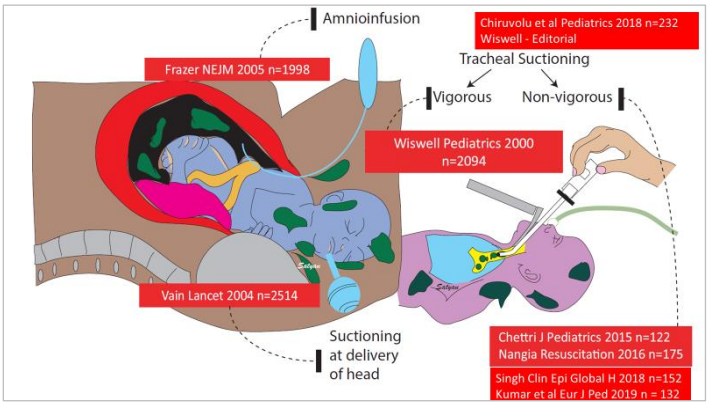


Slide 9

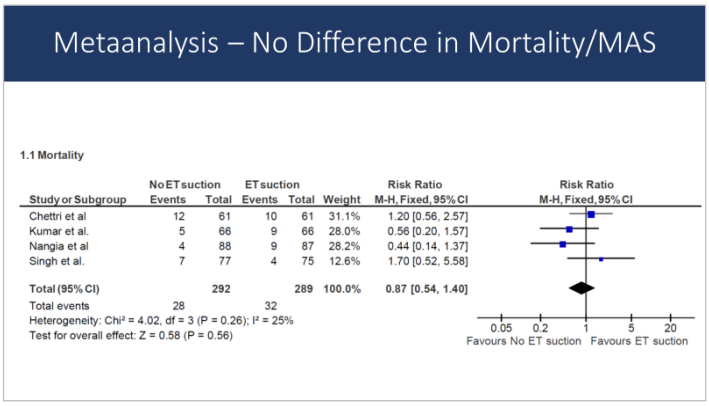
The mothers got amnioinfusion. As soon as the baby's head came out, there was a big fuss in suctioning the baby's head right away, and then [depending on] whether the babies were vigorous or non-vigorous, we would jump in and intubate these babies (that's how I learned my intubation, by the way). We would suction these babies and get all the meconium out, and that's what we did. But one after the other, wonderful, beautifully done, randomized trials have shown with large numbers—these are the number of babies enrolled in each of these trials—showed that one: this is not effective, this is not effective, this is not effective.

Finally, we landed in a situation where we used to recommend tracheal suction only for non-vigorous babies. Then 2 other trials came out, Chettri[7] and Nangia,[8] both conducted in India. Following the publication of these 2 trials, the AAP and NRP stopped recommending routine suctioning of the trachea for babies that were non-vigorous.

Neonatal Resuscitation: Scientific Basis



Slide 10



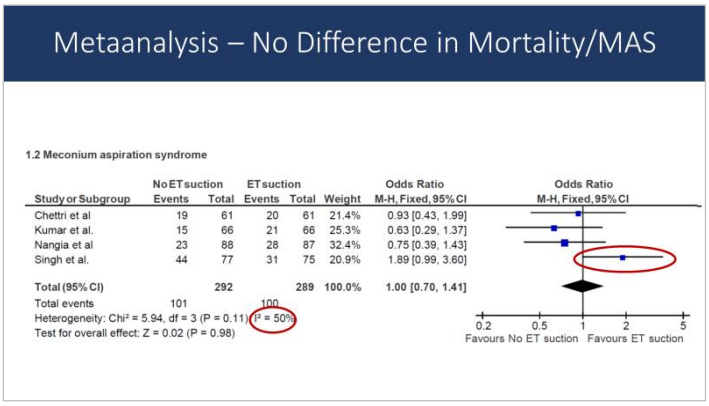
Slide 11

After the publication of these 2 trials, 2 more trials have come out: one is Singh[9] and the third is Kumar et al,[10] which literally came out last week. Both are randomized trials, and as you can see from the *n*, whereas these trials had close to 2,000 babies in each, all these trials put together probably have less than 5,500 babies in them. So, these are small trials conducted in single centers in India, and these trials show different results. In addition to these, there was a recent retrospective data analysis from *Pediatrics* by the MEDNAX group from Chiruvolu and colleagues, to which Tom Wiswell, who conducted the main trial, wrote an editorial,[11] which was a bit scathing to NRP, suggesting these guidelines were a bit too hasty in their recommendations.

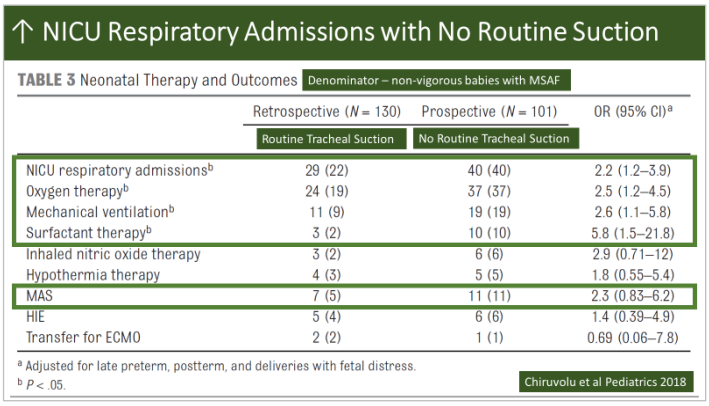
Let's look at these published trials—randomized control trials—to see where we are. This is a recent meta-analysis we put together last week using all the 4 trials. Like I said, the Kumar et al literally came out one week ago. As you can see from these trials,[10] if you look at mortality, there is absolutely no difference when you pool all the results, as to whether you suction the babies routinely or you do not suction these babies.

Now look at the incidence of meconium aspiration syndrome. Overall, there is no improvement either, but there is a significant degree of heterogeneity in these results. For example, the Singh et al study showed that if you do suction, you'll end up having lower incidence of meconium aspiration syndrome,[9] which barely missed significance in this particular condition, but the other 3 trials did not show that result. So, overall there is no real influence of meconium aspiration syndrome whether you suction these babies or not. But these trials are very difficult to conduct. For example, the experience of the resuscitator in the delivery room can vary. It can be an intern, it can be a nurse practitioner, it can be a neonatologist with 10 years of experience, and we don't even know if the intern intubated the trachea when they did the suctioning. So, there are lots of variability interpreting these results, making these studies very complicated.

Neonatal Resuscitation: Scientific Basis



Slide 12



Slide 13

This study really causes some concern. In addition to this, this trial came out: this is a retrospective review that came out in *Pediatrics* last year, by Arpitha Chiruvolu in 2018.[12] She showed that during the retrospective period when they were following the NRP 6th edition guidelines and were routinely suctioning all babies, during that period, the incidence of MAS [meconium aspiration syndrome] was around 5% among babies who were non-vigorous, born with meconium-stained amniotic fluid. On the other hand, when they stopped doing routine suctioning, the incidents of MAS went up to 11%, but this result was not statistically significant.

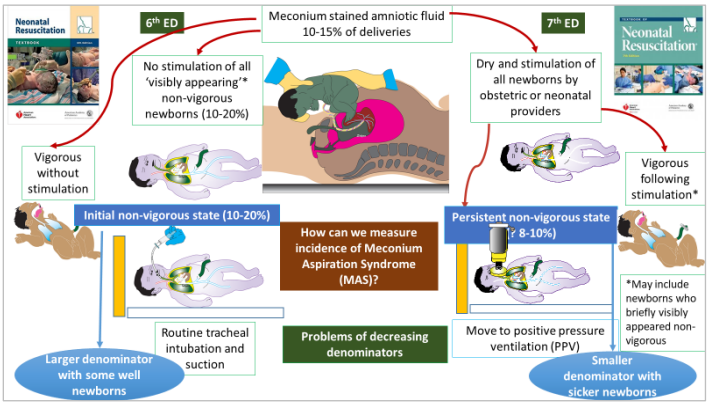
What was concerning in this paper was that although the meconium aspiration syndrome was not significantly different, the incidence of NICU respiratory admissions, use of oxygen, mechanical ventilation, and surfactant therapy, all of these significantly went up after stopping suctioning these babies. This was a big concern when this paper came out.

I want to remind you that the denominator in this study is babies who are not vigorous, born with meconium-stained amniotic fluid, because that's a very important factor here.

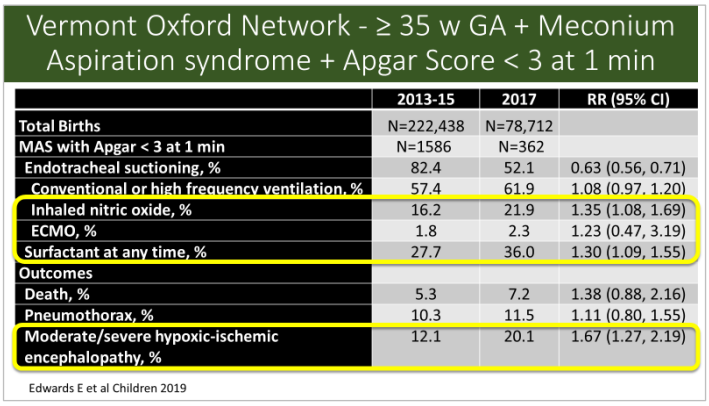
Let's say you are practicing NRP 6th edition way back in 2011, and now you're practicing in NRP 7th edition right now.[13] There's a big difference in how things are practiced before you get to the point of suctioning. For example, when we used to practice using old guidelines, as soon as the baby was born, if the baby was vigorous without stimulation, we left those babies alone. On the other hand, if the baby was visibly not vigorous, the incidence of which is close to 10%–20%, we went ahead and immediately intubated these babies and then suctioned the trachea.

Nowadays, what do we do? Every baby that's born, whether he is or not vigorous, we go ahead and stimulate these babies with tactile stimulation quite aggressively, and many of these babies turn vigorous, and they do quite well.

Neonatal Resuscitation: Scientific Basis



Slide 14



Slide 15

On the other hand, babies who go through this tactile stimulation and still remain in a persistent non-vigorous state, we consider these to be non-vigorous, and then intervene with positive pressure ventilation in these babies.

How do we measure the real incidence of meconium aspiration syndrome [MAS]? Because if you use this denominator [initial non-vigorous state (10%–20%)], it's a much larger denominator, and so the incidence of MAS is going to be lower. But, if you use this denominator [persistent non-vigorous state (8%–10%), this is a much smaller denominator, and so the incidence of MAS and respiratory distress is going to be higher. This is a huge challenge that many of us in resuscitation trials are facing. We're trying to address how to tackle this problem right now.

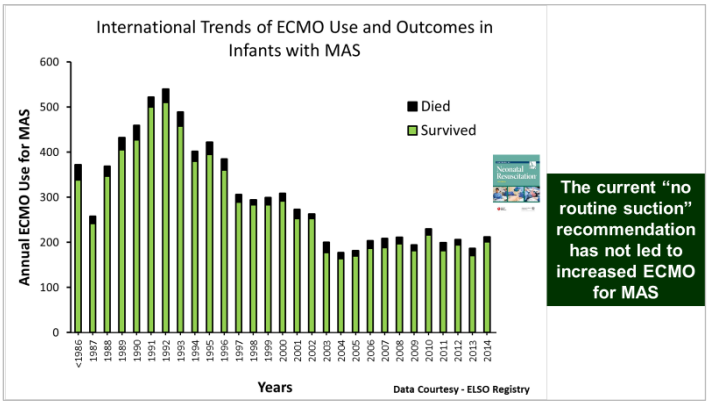
In fact, we pooled data from the Vermont Oxford Network to see what happens to your baby, who is greater than 35 weeks of gestation, with meconium aspiration syndrome, and has an Apgar score of less than 3 at 1 minute.

If you compare these babies when NRP 6th edition was being practiced, you will see that 12.1% of these babies developed moderate-to-severe hypoxic-ischemic encephalopathy. But, the same Apgar score of <3 at 1 minute in the new era means a totally different thing, because here we are stimulating the baby during the first minute, and in spite of that, the baby has not responded to stimulation and is still non-vigorous. Now the same baby has a 20.1% chance of developing moderate-to-severe HIE [hypoxic ischemic encephalopathy].

The denominator is different between this era [2013–2015] and *this* era [2017], and doing a comparison has become quite difficult. Similarly, you will notice that babies in the new era, who were called non-vigorous, tend to have higher use of inhaled nitric oxide and higher use of surfactant because these are sicker babies who failed to respond to simple, tactile stimulation, and continue to stay in a non-vigorous state. Basically, **there is an urgent need for a large multicenter randomized trial addressing suctioning vs non-suctioning in these babies**.

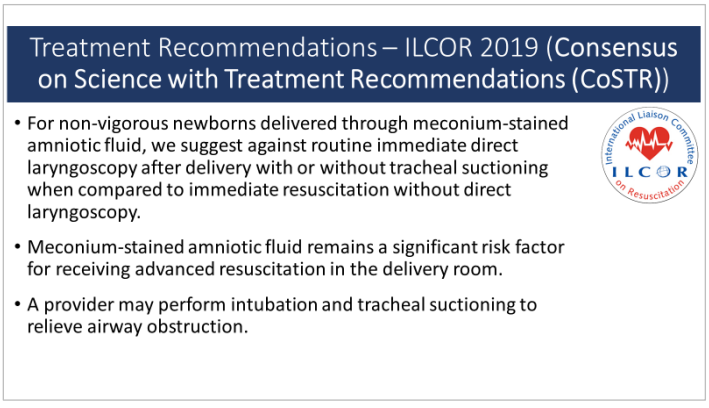
One bit of information that's reassuring is the incidence of ECMO [extracorporeal membrane oxygenation]—[the] use of ECMO throughout the international registry. Here is the incidence of ECMO for meconium aspiration syndrome, which had remained constant between 2003 and 2014

without any increase in incidents. With the publication of new guidelines, thankfully the incidence of ECMO for meconium aspiration syndrome has actually gone down, and this is reassuring. All we can say at this point is that the current "No Routine Suction" guidelines have not led to an increase in the use of ECMO for meconium aspiration syndrome.



Slide 16

These are the CoSTR or Consensus on Science with Treatment Recommendations that are published recently.[14] This basically says there is no point, there is no suggestion for immediate direct laryngoscopy, but it's important to remember that **if the baby's chest is not moving, then you should still continue trachea suctioning to relieve airway obstruction**.

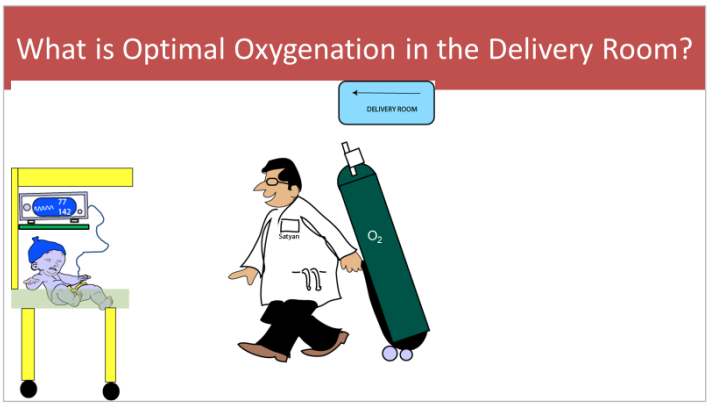


Slide 17

Don't throw away your meconium aspirators—you have no idea when you might need it. There might be situations where the baby's chest is not moving, and you may have to use this suction apparatus on babies with meconium-stained amniotic fluid.

Optimal Oxygenation

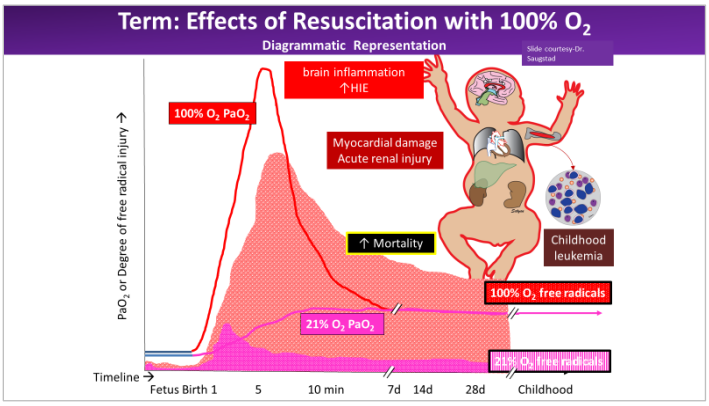
Moving along briefly [to talk] about room air. We all love using oxygen in the delivery room, and we have used it for many, many years, but it's important to remember that at least in term infants, if you use 21% oxygen, you increase PaO_2 to a modest degree.



Slide 18

This results in formation of a few free radicals in babies, which is tolerable by most term infants. On the other hand, if you use 100% O_2, there's a huge surge in PaO_2, resulting in a big surge of free radicals, and these free radicals have various consequences, like increasing brain inflammation, increasing HIE, myocardial damage, acute renal injury, and in some epidemiological studies, increased mortality and childhood leukemia.

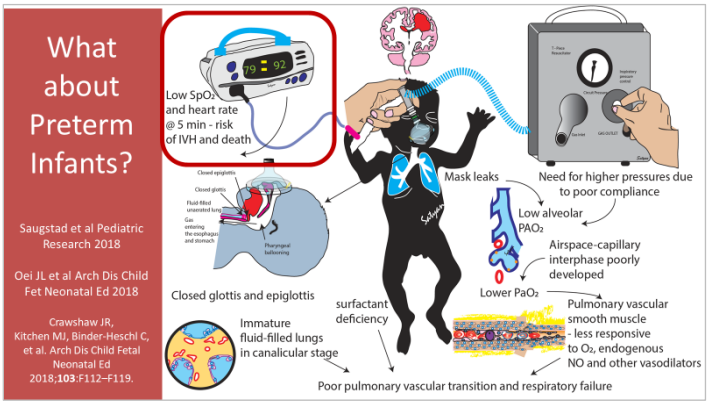
Neonatal Resuscitation: Scientific Basis



Slide 19

There are all these consequences that can happen in term babies, but in preterm babies, things are very different, as you heard earlier. In preterm babies, there are several problems. For example, if you can't get the Pulse Ox[imetry] in preterm babies by 5 minutes, about 80%, that's a big red flag, because these babies are at very high risk of mortality and developing IVH. You need to **do whatever it takes to achieve a saturation of 80% by 5 minutes in many of these preterm babies**.

Why do preterm babies behave so differently from term babies? Partly because they have mask leaks, and it's tough to aerate the lungs. The lungs have poor compliance; there is surfactant deficiency; there is air space; capillary interface is not very well developed. Many of these lungs are still in the canalicular stage, not even in the saccular stage.

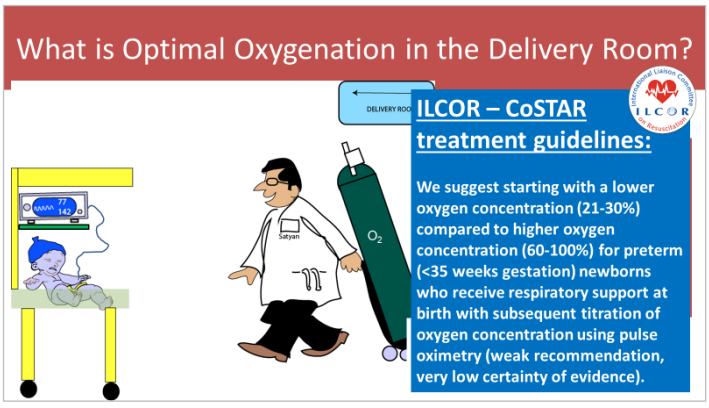


Slide 20

In addition, the pulmonary vasculature is not very responsive to oxygen; [it] might take more time to open up to a given amount of oxygen. There is immature fluid-filled lungs; there is surfactant deficiency; and over and above all in some of these nonresponsive babies who are not spontaneously breathing, the glottis is closed. No matter what you do with a bag mask ventilator, sometimes you will not be able to get air into the baby's lungs, and most of this might be going to the baby's esophagus and the stomach. These are the references for these studies.[15,16,17] The end result of all this is that there is poor pulmonary vascular transition and respiratory failure in many preterm babies.

Here is the current guideline for preterm babies that Ola Saugstad recommends:[18] more than 31 weeks use 21% O_2, 28–31 weeks use air or 30% O_2, in less than 28 weeks use 30% O_2. But the main thing here is that by 5 minutes, try to reach a sat[uration] of 80% or higher, and a heart rate of more than a hundred beats per minute.

This is slightly different from what was recommended by ILCOR[15] [International Liaison Committee on Resuscitation]. That we all had a chance to comment on, which basically concluded saying that anywhere from 21%–30% in less than 35 weeks is what is suggested. But the evidence for this is weak. This is a weak recommendation with a very low certainty of evidence, so we are stuck in this particular situation for the time being.

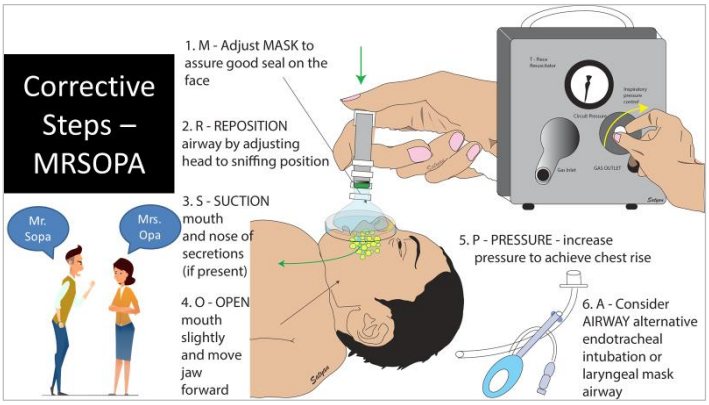


Slide 21

Neonatal Resuscitation: Scientific Basis

MR SOPA Guidelines

Then we have the MR SOPA guidelines that many of you are very familiar with.[19] In fact, it's a huge controversy as to whether we should call it MR SOPA or MRS OPA, because there's a huge gender variation here. Unfortunately being a member of the NRP, I have to side with men here, and call it MR SOPA, mainly because once you adjust the mask, and get a good seal, and reposition and put the head in sniffing position, you're supposed to use some ventilator breaths before you move on to suction. There is a pause between MR and SOPA. So, this is more correct. Sorry for the women in the audience.

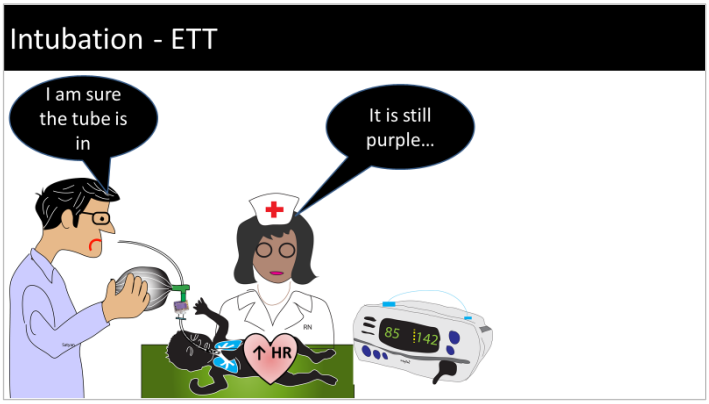


Slide 22

This is what we use. But the main thing is that if these things are not working, you need to go to an alternate airway as soon as you can in these babies.

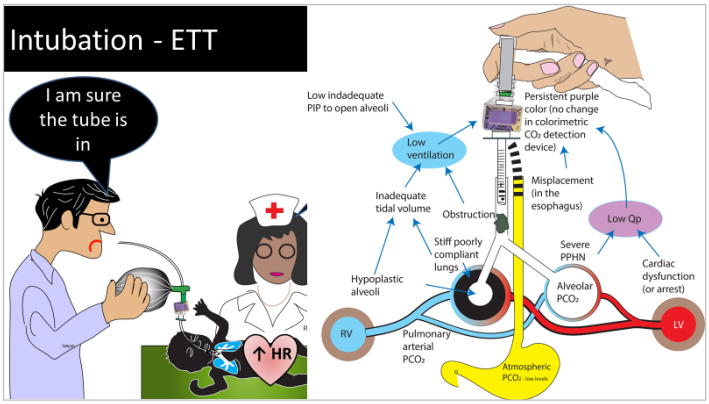
Proper Intubation

Talking about intubation, one controversial thing I always come across is, for example, last week when I was in service, I had a baby who was 23-weeks' gestation—barely 23 weeks, and I tubed the kid, and I knew that the tube was in but the capnography meter was not turning purple. I said, "I'm sure the tube is in." And my nurse was saying, *"Yeah, right. The thing is still purple, so you're not in."* This is a common situation that we come across. I have to say that if the heart rate is increasing, and if the pulse oximetry is getting better, and you start seeing some chest rise, it might take a little time for this thing to turn purple.



Slide 23

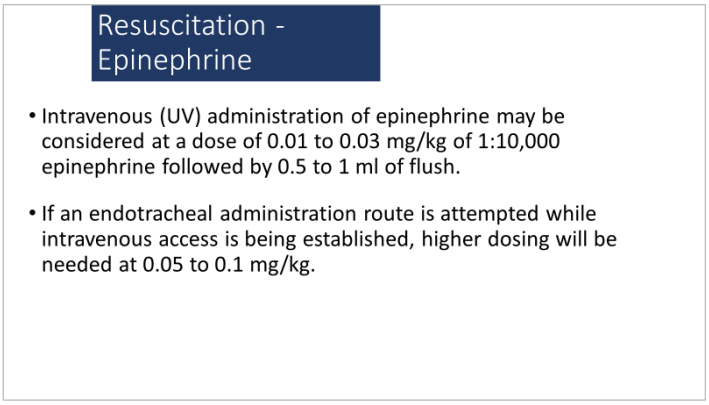
This happens in 2 specific situations. One, when the alveolar ventilation is low—as can happen with extreme prematurity or hyperplastic alveoli, or when the pulmonary blood flow is really low. Because if you don't have blood flow coming to the lung, there is nobody delivering carbon dioxide to the alveoli. This can happen in some cases of severe PPHN or cardiac dysfunction. **If your heart rate is going up, and the chest is rising, and if your pulse ox is getting better, wait for a few seconds to see if this thing will turn purple. Don't jump in and take the tube out in this situation.** But remember, in most situations when it's not turning yellow, it means that your tube is in the esophagus, and that's something you obviously need to correct.



Slide 24

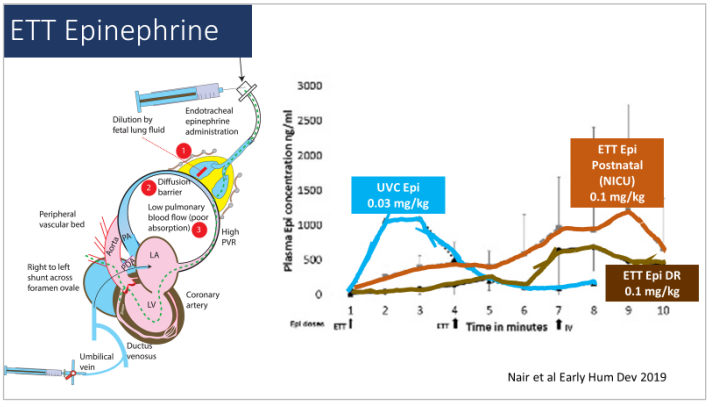
Epinephrine Dosing

I'll briefly move along to epinephrine in the last 5 minutes of my presentation. Right now, the recommendations suggest we try to use intravenous administration of epinephrine at a dose of 0.01 mg/kg–0.03 mg/kg of 1:10,000 epinephrine followed by 0.1–1 mL flush. This is the recommended route. But if you are working on placing the UV line, and if you already have an endotracheal tube in place, it's okay to use the ET tube for a higher dose of 0.05 mg/kg–0.1 mg/kg. This is what we do at this time. Let me show you some recent data from my lab—from my colleagues—which questions some of these things.



Slide 25

In the newborn period, a newly born infant has a lot of lung liquid still left, even after the vaginal squeeze, by the way. You have close to anywhere from 10 mL–30 mL per kg of lung liquid in this situation. When you deliver epinephrine into this fluid-filled lung, it's diluted, to a certain extent, and doesn't easily cross over and reach the heart and the circulation. Here you see some data showing that if you give UVC [umbilical venous catheter] epinephrine, you get a nice quick surge in epinephrine, and that helps kickstart the heart. On the other hand, if you use epinephrine into your fluid-filled lung, you barely get any increase in epinephrine levels until the baby starts having spontaneous circulation. Then, all this epinephrine sitting in the lung liquid gets absorbed, and you get a layered surge in epinephrine. That's what happens in babies at birth with endotracheal epinephrine.

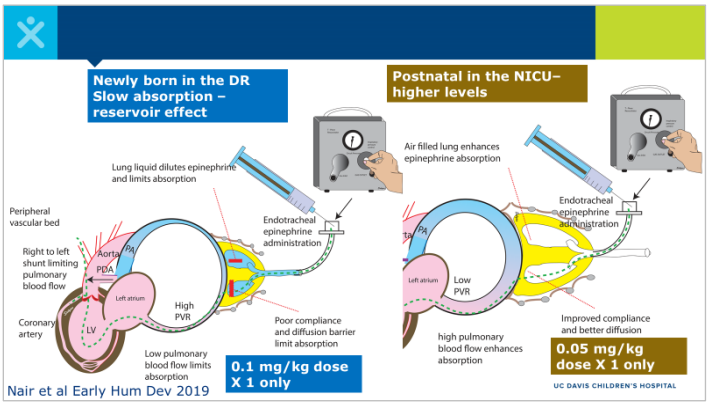


Slide 26

On the other hand, when you give epinephrine to your baby during the postnatal period, for example, you have a 3-day old sitting in the NICU, who goes into [cardiac] arrest. You use endotracheal epinephrine in that situation—then there is no lung liquid—and you get much higher levels with epinephrine postnatally than you do prenatally.

What we recommend at this time—this is a personal recommendation, not from the AAP—in the newly born period, don't waste time using 0.05 mg/kg. Go to the higher end of the dose. Use 0.1 mg/kg per dose. Just use it once. Make sure you get a UV line before you use it for the second time, because if you put too much of epinephrine down here that has a slow absorption, there is slower effect, and [it] can jump into the circulation once spontaneous circulation is established.

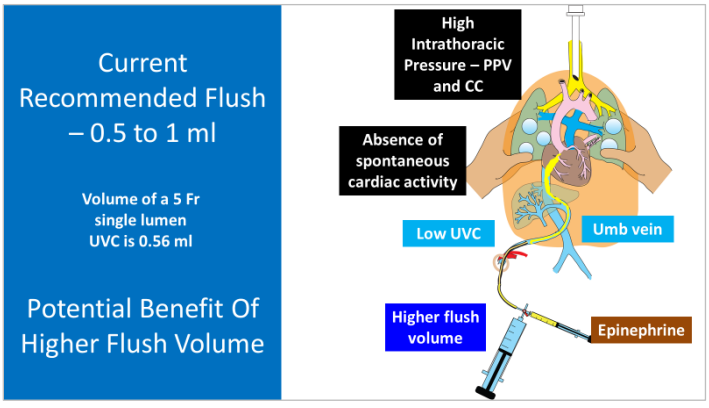
Neonatal Resuscitation: Scientific Basis



Slide 27

On the other hand, if you're using it postnatally, all you need to do is try to use the lower end, because there is no lung liquid here, and there's lots of pulmonary circulation, and this can be absorbed much more efficiently during the postnatal period.

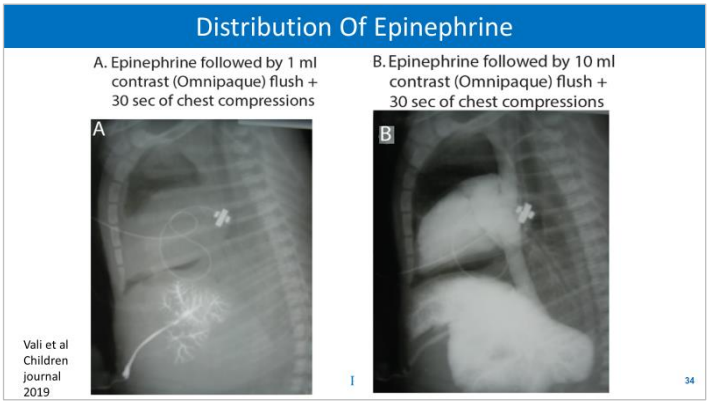
What about the flush? We currently recommend 0.5 mL–1.0 mL flush following epinephrine. This is because when you look at the 5 Fr single lumen umbilical venous catheter, the volume of this catheter is 0.56 mL. What you're trying to do with this flush is to push the epinephrine from the umbilical vein catheter into the baby. What we noticed—at least in lambs—is that the resistance in the ductus venosus is usually a little higher. It's not easy to overcome that just with 0.5 mL–1 mL of flush.



Slide 28

Our hypothesis is that if you have a low UVC in an umbilical vein, and if there is absence of spontaneous cardiac activity, and you're providing high intrathoracic pressure with chest compressions, giving 0.5 mL of flush might not be adequate. We are looking for evidence to show that [if] you use the higher flush, that might be enough to propel epinephrine into the baby's heart.

Here is some data to show you. This is a lamb, lateral chest X-ray of a lamb, where we placed a low umbilical venous line and injected epinephrine followed by 0.5 mL of flush and did chest compressions for 30 seconds. As you can see, most of the epinephrine sits inside the liver and doesn't enter the cardiac circulation. On the other hand, if you use 10 mL flush, there's a lot better absorption of epinephrine, and it enters the baby's heart much more efficiently.



Slide 29

We recently did a randomized trial in lambs, these are not human data, these are from lambs, to show that using a high dose 0.03 mg/kg with a high flush of approximately 3 mL/kg results in much better spontaneous recovery for these babies. Especially with the first dose, almost 80% of these lambs could be recovered, and these are all lambs with complete cardiac arrest.

Neonatal Resuscitation: Scientific Basis

Parameter	Low dose (0.01 mg/kg)n=11		High dose (0.03 mg/kg)n=12	
	Low flush(6)	High flush(5)	Low flush(7)	High flush(5)
ROSC achieved n(%)	2 (33%)	2 (40%)	5 (71%)	5 (100%)
ROSC with 1st dose of epi	1 (16.7%)	2 (40%)	3 (42%)	4 (80%) !
Median time to ROSC from PPV (sec)	697 (536-858)^	397 (396-398)	480 (372-600)	420 (360-420)
Median time to ROSC from epi & flush (sec)	127 (101-153)^	47 (41-53)	90 (60-120)	36(30-60)

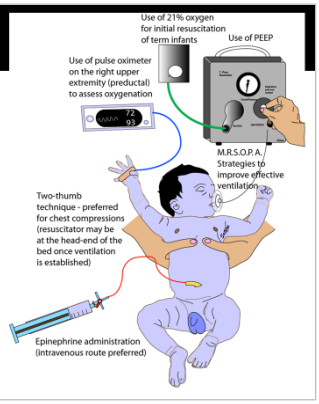
ROSC: Return of Spontaneous Circulation
^ p<0.05 low dose low flush vs high dose high flush. (unpaired t test)
!p<0.05 high dose high flush vs low dose low flush

Sankaran et al PAS 2019

Slide 30

Summary

- Ventilation of the lungs is the key to neonatal resuscitation
- Increasing heart rate is the most important sign of effective resuscitation
- Avoid cord milking in extremely preterm infants
- 21% oxygen may not be adequate for initial resuscitation of extremely preterm infants
- Epinephrine: avoid multiple ET doses
- UVC epinephrine: 0.03mg/kg → 3 ml/kg flush



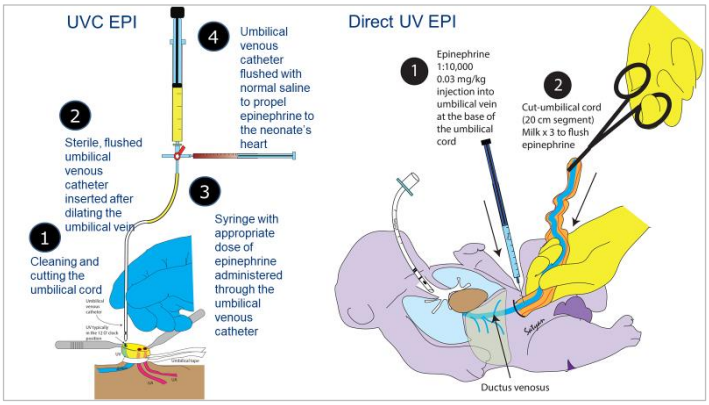
Slide 31

Right now we personally recommend **0.03 mg/kg of epinephrine or 0.3 mL/kg of epinephrine, followed by a 3 mL/kg flush**, which is approximately 10 mL in term babies.[20] Remember, in preterm babies, use a smaller amount of flush, so **if you have a 500-g baby, a 1.5 mL flush is more than adequate**. In some babies, more flush might be required. Again, this is not an AAP recommendation. This is something that I personally use in the delivery room.

Conclusion

To summarize, ventilation of lungs is the key to neonatal resuscitation, and increasing heart rate is the most important sign of effective resuscitation. Avoiding cord milking in extremely preterm infants is important, and 21% O_2 might not be adequate for initial resuscitation of extremely preterm infants. With epinephrine, avoid multiple endotracheal doses. With umbilical vein epinephrine, use 0.03 mg/kg followed by a decent flush, and that might be much more effective in resuscitation.

We recently got a grant to study the use of epinephrine in a new mechanism. All of you have seen that it takes a few minutes to prepare a catheter and give UVC epinephrine. So, what we're studying right now is to use a cord that's around 20 cm long; cut a long cord when baby's asphyxiated, and instead of using a catheter, directly inject epinephrine into the umbilical vein and subsequently milk the cord 3 times.



Slide 32

This appears to be a fairly effective mechanism, and we are now conducting a randomized trial to evaluate this particular study.

Neonatal Resuscitation: Scientific Basis

Abbreviations

Apgar	**A**ppearance, **P**ulse, **G**rimace, **A**ctivity, and **R**espiration	**NRP**	Neonatal Resuscitation Program
BPD	bronchopulmonary dysplasia	**PaO_2**	partial pressure of oxygen
DCC	delayed cord clamping	**PALS**	Pediatric Advanced Life Support
ECMO	extracorporeal membrane oxygenation	**PICU**	pediatric intensive care unit
ETT	endotracheal tube	**SAIL**	Sustained Aeration Inflation for Infant Lungs clinical trial
FiO_2,	fraction of inspired oxygen in the air	**SI**	sustained inflation
HIE	hypoxic ischemic encephalopathy	**SpO_2**	peripheral capillary oxygen saturation, an estimate of the amount of oxygen in the blood
ICH	intracerebral hemorrhage	**TORPEDO**	Targeted Oxygen in the Resuscitation of Preterm Infants clinical trial
IVH	intraventricular hemorrhage	**UMC**	umbilical cord milking
MAS	meconium aspiration syndrome	**UVC**	umbilical venous catheter
MSAF	meconium-stained amniotic fluid		

1. Oei JL, Saugstad OD, Lui K, et al. Targeted oxygen in the resuscitation of preterm infants, a randomized clinical trial. *Pediatrics*. 2017;139(1). pii: e20161452. doi:10.1542/peds.2016-1452
2. Foglia EE, Owen LS, Thio M, et al. Sustained Aeration of Infant Lungs (SAIL) trial: study protocol for a randomized controlled trial. *Trials*. 2015;16:95. doi:10.1186/s13063-015-0601-9
3. Tarnow-Mordi W, Morris J, Kirby A, et al; Australian Placental Transfusion Study Collaborative Group. Delayed versus Immediate Cord Clamping in Preterm Infants. *N Engl J Med*. 2017;377(25):2445-2455. doi:10.1056/NEJMoa1711281
4. Katheria A, Reister F, Essers J, et al. Association of umbilical cord milking vs delayed umbilical cord clamping with death or severe intraventricular hemorrhage among preterm infants. *JAMA*. 2019;322(19):1877-1886. doi:10.1001/jama.2019.16004
5. Andersson O, Rana N, Ewald U, et al. Intact cord resuscitation versus early cord clamping in the treatment of depressed newborn infants during the first 10 minutes of birth (Nepcord III) - a randomized clinical trial. *Matern Health Neonatol Perinatol*. 2019;5:15. doi:10.1186/s40748-019-0110-z
6. Nagano N, Saito M, Sugiura T, Miyahara F, Namba F, Ota E. Benefits of umbilical cord milking versus delayed cord clamping on neonatal outcomes in preterm infants: A systematic review and meta-analysis. *PLOS One*. 2018;13(8):e0201528. doi:10.1371/journal.pone.0201528 eCollection 2018.
7. Chettri S, Adhisivam B, Bhat BV. Endotracheal suction for nonvigorous neonates born through meconium stained amniotic fluid: A randomized controlled trial. *J Pediatr.* 2015;166(5):1208-1213.e1. doi:10.1016/j.jpeds.2014.12.076
8. Nangia S, Sunder S, Biswas R, Saili A. Endotracheal suction in term non vigorous meconium stained neonates-A pilot study. *Resuscitation*. 2016;105:79-84. doi:10.1016/j.resuscitation.2016.05.015

9. Singh SN, Saxena S, Bhriguvanshi A, Kuma M, Sujata C. Effect of endotracheal suctioning just after birth in non-vigorous infants born through meconium stained amniotic fluid: A randomized controlled trial. *Clin Epi Global H*. 2019;165–170.
10. Kumar A, Kumar P, Basu S. Endotracheal suctioning for prevention of meconium aspiration syndrome: a randomized controlled trial. *Eur J Pediatr*. 2019;178(12):1825-1832. doi:10.1007/s00431-019-03463-z
11. Wiswell TE. Appropriate Management of the Nonvigorous meconium-stained neonate: An unanswered question. *Pediatrics*. 2018;142(6). pii: e20183052. doi:10.1542/peds.2018-3052
12. Chiruvolu A, Miklis KK, Chen E, Petrey B, Desai S. Delivery room management of meconium-stained newborns and respiratory support. *Pediatrics*. 2018;142(6). pii: e20181485. doi:10.1542/peds.2018-1485
13. NRP Instructor Update. Summary of the Revised Neonatal Resuscitation Guidelines 7th Edition. 2015; 24(2). Available at https://www.aap.org/en-us/Documents/nrp_newsletter_2015_fallwinter.pdf
14. Escobedo MB, Aziz K, Kapadia VS, et al. 2019 American Heart Association focused update on neonatal resuscitation: An update to the American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Pediatrics*. 2020;145(1) e20191362. doi:https://doi.org/10.1542/peds.2019-1362
15. Escobedo MB, Aziz K, Kapadia VS, et al. 2019 American Heart Association focused update on neonatal resuscitation: An update to the American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Pediatrics*. 2020;145(1) e20191362. doi:https://doi.org/10.1542/peds.2019-1362
16. Oei JL, Finer NN, Saugstad OD, et al. Outcomes of oxygen saturation targeting during delivery room stabilisation of preterm infants. *Arch Dis Child Fetal Neonatal Ed.* 2018;103(5):F446-F454. doi:10.1136/archdischild-2016-312366
17. Crawshaw JR, Kitchen MJ, Binder-Heschl C, et al. Laryngeal closure impedes non-invasive ventilation at birth. *Arch Dis Child Fetal Neonatal Ed*. 2018;103(2):F112-F119. doi:10.1136/archdischild-2017-312681
18. Saugstad OD, Oei JL, Lakshminrusimha S, Vento M. Oxygen therapy of the newborn from molecular understanding to clinical practice. *Pediatr Res*. 2019;85(1):20-29. doi:10.1038/s41390-018-0176-8
19. Sharma V, Lakshminrusimha S, Carrion V, Mathew B. Resuscitator's perceptions and time for corrective ventilation steps during neonatal resuscitation. *Resuscitation*. 2015;91:63-6. doi:10.1016/j.resuscitation.2015.03.008
20. Vali P, Sankaran D, Rawat M, Berkelhamer S, Lakshminrusimha S. Epinephrine in neonatal resuscitation. *Children (Basel).* 2019;6(4). pii: E51. doi:10.3390/children6040051